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ORIGINAL REPORT

Six Cycles of Doxorubicin and Cyclophosphamide or Paclitaxel Are Not Superior to Four Cycles As Adjuvant Chemotherapy for Breast Cancer in Women With Zero to Three Positive Axillary Nodes: Cancer and Leukemia Group B 40101

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ABSTRACT

Purpose
The ideal duration of adjuvant chemotherapy for patients with lower risk primary breast cancer is not known. Cancer and Leukemia Group B trial 40101 was conducted using a phase III factorial design to define whether six cycles of a chemotherapy regimen are superior to four cycles. We also sought to determine whether paclitaxel (T) is as efficacious as doxorubicin/cyclophosphamide (AC), but with reduced toxicity.

Patients and Methods
Between 2002 and 2008, the study enrolled women with operable breast cancer and zero to three positive nodes. Patients were randomly assigned to either four or six cycles of either AC or T. Study stratifiers were estrogen receptor/progesterone receptor (ER/PgR), human epidermal growth factor receptor 2 (HER2), and menopausal status. After 2003, all treatment was administered in dose-dense fashion. The primary efficacy end point was relapse-free survival (RFS).

Results
A total of 3,171 patients were enrolled; 94% were node-negative and 6% had one to three positive nodes. At a median follow-up of 5.3 years, the 4-year RFS was 90.9% and 91.8% for six and four cycles, respectively. The adjusted hazard ratio (HR) of six to four cycles regarding RFS was 1.03 (95% CI, 0.84 to 1.28; $P = .77$). The 4-year OS was 95.3% and 96.3% for six and four cycles, respectively, with an HR of six to four cycles of 1.12 (95% CI, 0.84 to 1.49; $P = .44$). There was no interaction between treatment duration and chemotherapy regimen, ER/PgR, or HER2 status on RFS or OS.

Conclusion
For women with resected primary breast cancer and zero to three positive nodes, we found no evidence that extending chemotherapy regimens of AC or single-agent T from four to six cycles improves clinical outcome.

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INTRODUCTION

The ideal duration of adjuvant therapy for women with low-risk primary breast cancer is not known. National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-15 compared six cycles of cyclophosphamide, methotrexate, and fluorouracil (FU; CMF) with four cycles of doxorubicin and cyclophosphamide (AC) and found them to be equivalent, and subsequent clinical trials have used both of these regimens as control arms.[1] Four cycles of AC was the basis for Cancer and Leukemia Group B (CALGB) and NSABP trials that examined the potential benefit of adding a taxane to the treatment.[2,3] Six cycles of CMF was the control arm of the study comparing six cycles of cyclophosphamide, doxorubicin, and FU (CAF) in women with node-negative breast cancer by the North American Breast Intergroup and

Southwest Oncology Group.[4] More recently, four cycles of AC has been the control arm when testing taxane-containing regimens, such as doxorubicin-docetaxel by Goldstein et al[5] and docetaxel-cyclophosphamide by Jones et al.[6] Martin et al[7] compared six cycles of CAF with six cycles of docetaxel, doxorubicin, and FU for women with node-negative breast cancer.

To address the question of treatment duration, the CALGB, together with Eastern Cooperative Oncology Group, Southwest Oncology Group, and North Central Cancer Treatment Group, initiated a randomized, phase III, 2 × 2 factorial trial (CALGB 40101) designed to assess the first factor (six cycles of therapy *v* four cycles of therapy) and the second factor (single-agent T *v* AC). This article describes the results of the comparison of six cycles versus four cycles of therapy.

PATIENTS AND METHODS

The trial was initiated in 2002 as a 2 × 2 factorial design comparing longer versus shorter therapy and AC versus single-agent T in women with node-negative disease. AC was administered once every 3 weeks for four (12 weeks) or six (18 weeks) cycles and T was administered weekly for 12 or 18 weeks (3 weeks of T was considered one cycle). Five hundred seventy-one patients were accrued using this trial design. In 2003, when the results of CALGB 9741 showed the superiority of dose-dense therapy administered every 2 weeks compared with every 3 weeks,[8] our trial was amended so that both AC and T were administered every 2 weeks for four or six cycles. AC was administered as doxorubicin 60 mg/m^2 and cyclophosphamide as 600 mg/m^2. Paclitaxel was administered as 80 mg/m^2 when given weekly and 175 mg/m^2 when given every 2 weeks.

In 2005, women with one to three positive axillary nodes were permitted onto the study. In February 2008, the six-cycle arms were closed to accrual with 3,171 patients enrolled onto the study. The study design then changed to a two-arm study comparing four cycles of AC with four cycles of T. The study was permanently closed to accrual in July 2010 owing to declining enrollment, at which time 3,871 patients were enrolled.

Hormone therapy (tamoxifen for any patient or aromatase inhibitors in postmenopausal women) was recommended for patients with hormone-receptor–positive tumors. After 2005, trastuzumab was recommended for women with human epidermal growth factor receptor 2 (HER2) –positive tumors. Women randomly assigned to receive AC were recommended to start trastuzumab after the conclusion of AC, and women randomly assigned to receive T could initiate trastuzumab concurrently with T or after completion of T.

Radiation therapy was required for women undergoing breast-conserving surgery, though the type of radiation (whole breast, partial breast, implant, and so on) was determined by the treating physicians. Postmastectomy radiation could be administered at the discretion of the treating physicians.

Patients must have been enrolled and received random assignment within 84 days of their last breast surgery, and treatment had to be initiated within 7 days of random assignment. Stratification factors included menopausal status, hormone-receptor status, and HER2 status.

Primary objectives of the study were to test the superiority of six cycles of therapy over four cycles of therapy and the equivalence of T compared with AC, both in regard to relapse-free survival (RFS). Secondary objectives included the same comparisons in regard to overall survival (OS). Other secondary objectives included the evaluation of toxicities for AC versus T and six cycles versus four cycles of therapy and the induction of menopause in premenopausal women by treatment arm. There were two companion studies designed to accompany the parent study. One was a quality of life companion trial designed to study the impact of short- and long-term toxicities on quality of life by treatment agent and duration. The second study was a pharmacogenomic companion study designed to assess whether germline polymorphisms would influence toxicity for AC or T and survival outcomes. Each patient gave written approval on a protocol-specific, institutional review board–approved, consent form.

The primary study end point was RFS, defined according to standardized efficacy end point criteria, measured from study entry until local recurrence, distant relapse, or death without relapse, whichever occurred first.[9] All second cancer primaries, regardless of site, were considered adverse events and not failures in RFS. Surviving patients who were relapse-free were censored at the date they were last known to be free from their primary breast cancer. The secondary end point of OS was measured from study entry until death from any cause; surviving patients were censored at the date of last contact. Death as a result of acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) was considered treatment-related.

The primary comparison of treatment length used proportional hazards modeling that adjusted for tumor size, number of involved lymph nodes, hormone receptor status (either estrogen-receptor [ER] or progesterone-receptor positive *v* ER and progesterone-receptor negative), and menopausal

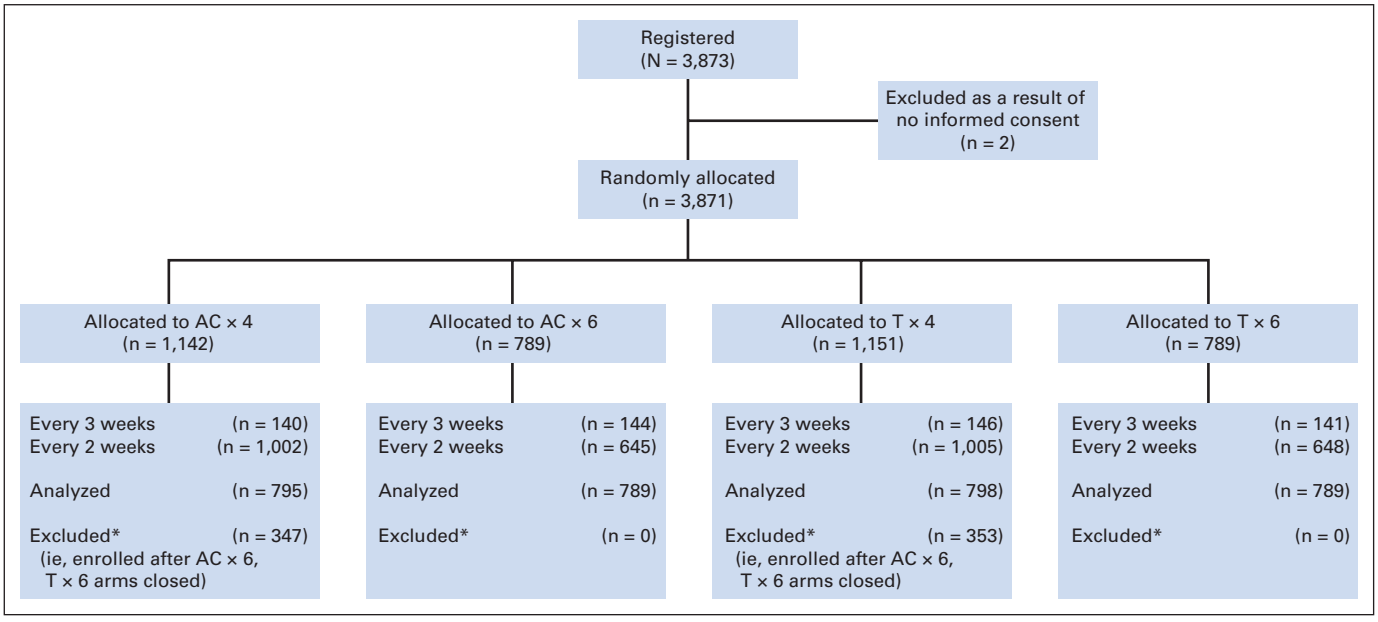

Fig 1. CONSORT diagram showing patients registered, treatment arm assignments, and exclusions. AC, doxorubicin and cyclophosphamide; T, paclitaxel.

Table 1. Patient Characteristics

Characteristic	Treatment Length (%)		
	Four Cycles (n = 1,593)	Six Cycles (n = 1,578)	Total (%; N = 3,171)
Age ≥ 50 years	59	59	59
Nonwhite	16	15	15
Premenopausal	44	44	44
Node-negative	94	93	94
Tumor size ≤ 2 cm	66	62	64
ER-positive tumors	65	64	64
HER2-negative tumors	77	77	77
High grade	47	48	47

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

status. The statistical significance of each variable included in the models was assessed using the corresponding Wald χ^2 statistics. Hazard ratios (HR) and their 95% CI were obtained from multivariate proportional hazards models. RFS and OS distributions were estimated using the Kaplan-Meier product-limit technique.[10] Log-rank tests compared distributions of two or more groups.[11] 95% CIs of time-to-event variables were measured using the Hosmer and Lemeshow method.[12] Efficacy analyses used an intention-to-treat approach. All adverse events were reported using National Cancer Institute common toxicity criteria.[13] *P* values are two-sided.

To test the superiority in RFS of six over four cycles of protocol therapy, the study was powered against a two-sided ($\alpha = .05$) alternative hypothesis with an HR of 0.77 corresponding to a decrease of 23% in hazard of relapse attributed to six cycles. With a target accrual of 4,646 patients accrued over 29 months and four additional years of follow-up, there was 91% power to detect the stated difference. Under the alternative hypothesis, the expected total number of events was 567.

In accordance with National Cancer Institute policy, our study was monitored every 6 months by an independent data and safety monitoring board (DSMB) beginning in November 2002. Preplanned interim analyses to stop study early for the superiority of six over four cycles used symmetric O'Brien-Fleming bounds for a two-sided hypothesis and a Lan-DeMets spending function. Early stopping for futility was not planned. The first formal interim analysis, scheduled at 10% of the total expected events, was conducted in June 2006. Thereafter, interim analyses were conducted every 6 months until June 2008. In June 2010, the DSMB released the results for the four- versus six-cycle comparison.

Study data were collected by CALGB Data Operations and stored in the CALGB database. All analyses were conducted by CALGB statisticians. Data were current as of August 2011.

RESULTS

Between study activation in May 2002 and closure of the six-cycle arms in February 2008, a total of 3,171 patients were accrued. These patients comprise the assessable sample in our article. In June 2010, the DSMB released data for the six- versus four-cycle comparison. Although no observed statistics crossed the interim superiority boundaries, the Bayesian predictive probability for concluding superiority of the six-cycle regimens over the four-cycle regimens was .001. Specifically, based on observed available data, the probability of concluding superiority if the trial had run to completion by achieving the target accrual of 4,646 patients and expected 567 total events was only .001. This probability assumed exponential survival with independent and noninformative prior distributions about the parameters and was based on 283 events and an observed HR of 6:4 cycles of 1.12 (95% CI, 0.89 to 1.42). The prediction assumed that the eventual conclusion would have a two-sided $\alpha$of .05 as specified in the protocol.

Patient Characteristics

Patients enrolled, patients excluded from analysis and the reasons for their exclusion, and the final numbers analyzed are shown in Figure 1. The patient characteristics are well balanced between study arms as listed in Table 1. Sixty-four percent of patients had T1 tumors, 64% had ER-positive tumors, 23% had tumors that were positive for HER2 overexpression or amplification, 47% had high-grade tumors, and 94% of patients had node-negative disease. Forty-four percent of patients in both groups were premenopausal. At the time of reporting, 45 patients (1%) were lost to follow-up, and 57 patients (2%) had withdrawn consent to receive follow-up. The median follow-up period for surviving patients was 5.3 years, with a maximum of 8.9 years.

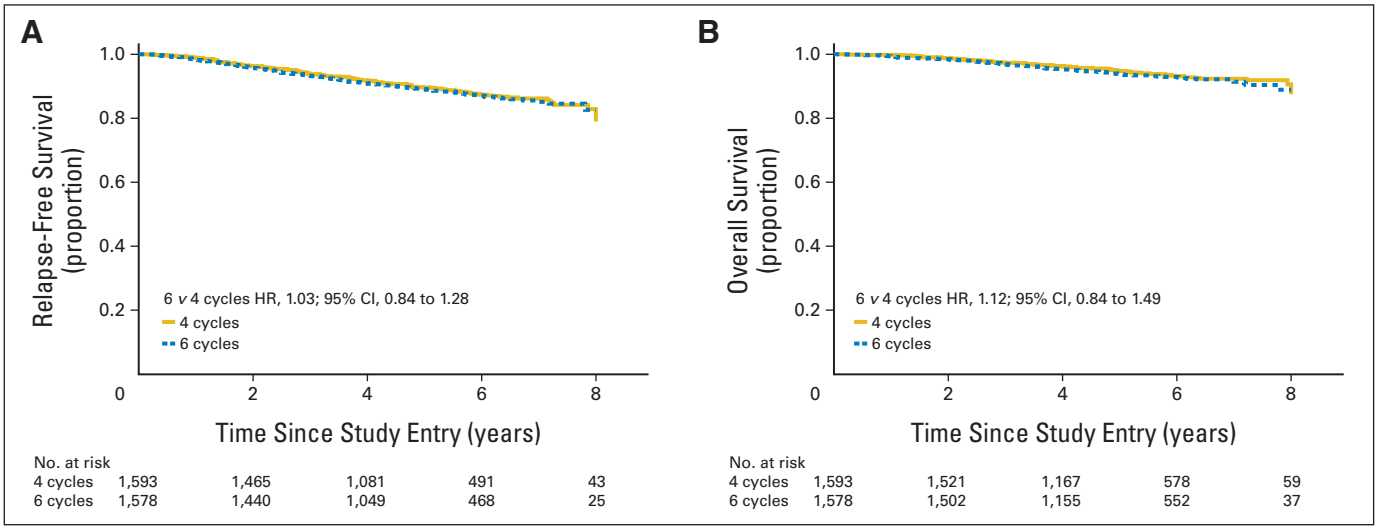

Fig 2. (A) Relapse-free and (B) overall survival comparing four cycles versus six cycles of therapy. HR, hazard ratio.

Table 2. Multivariate Proportional Hazards Models: Observed Effects on RFS and OS

Variable	Comparison of Worse:Better for HR	RFS (n = 3,160)*			OS (n = 3,160)†		
		HR	95% CI	*P*	HR	95% CI	*P*
Treatment duration, cycles	6:4	1.03	0.84 to 1.28	.77	1.12	0.84 to 1.49	.44
Tumor size, cm	2:1.5	1.16	1.09 to 1.22	< .001	1.21	1.12 to 1.30	< .001
No. of positive nodes	2:0	1.34	0.76 to 2.33	.31	1.77	0.88 to 3.56	.11
Hormone receptor	Neg:pos	1.95	1.57 to 2.42	< .001	2.73	2.04 to 3.65	< .001
Menopausal status	Post:pre	1.13	0.91 to 1.41	.27	1.56	1.51 to 2.12	.004

Abbreviations: HR, hazard ratio; neg, negative; OS, overall survival; pos, positive; post, postmenopausal; pre, premenopausal; RFS, relapse-free survival.
*11% events.
†6% events.

Efficacy End Points

The 4-year RFS was 90.9% for patients randomly assigned to six cycles of therapy and 91.8% for patients randomly assigned to four cycles. The 4-year OS for patients randomly assigned to six cycles of therapy was 95.3% and 96.3% for patients randomly assigned to four cycles of therapy. Kaplan-Meier curves for these groups are illustrated in Figure 2. Results of multivariate proportional hazards modeling indicated that six cycles of therapy was not superior to four cycles for either RFS or OS after adjusting for the effects of tumor size, number of positive nodes, hormone receptor status, and menopausal status. The observed adjusted HR of 6:4 cycles for RFS was 1.03 (95% CI, 0.84 to 1.28; $P = .77$) and for OS was 1.12 (95% CI, 0.84 to 1.49; $P = .44$; Table 2).

Unplanned subset analyses were performed based on tumor ER and HER2 status. There was no interaction between the number of cycles of therapy and any of these variables, suggesting that no subgroup benefitted from a longer period of therapy.

Although the DSMB has not released data for the comparison of AC versus T, it has informed us that there was no interaction between treatment duration and chemotherapy regimen. The above-referenced predictive probability calculation of .001 for eventual superiority of six cycles versus four cycles was based on the assumption that there was in fact no interaction.

Toxicities

Patients' principal toxicities are listed in Table 3. As expected, hematologic toxicity was most pronounced in the AC study arms compared with the T arms and was slightly more common in those patients treated with six cycles of AC. Patients receiving six cycles of AC demonstrated 11% grade 3 and 23% grade 4 neutropenia. Neutropenia and fever (grades 3 and 4) occurred in 6% of each of the AC study arms. Neuropathy was most common in the paclitaxel arms compared with the AC arms, with grade 3 sensory toxicity occurring in 4% of those patients treated with four cycles of paclitaxel and 10% of those treated with six cycles. Grade 3 motor neuropathy occurred in 2% of those patients who received four cycles of paclitaxel and in 3% of patients receiving six cycles. Less than 1% of patients reported grade 4 neuropathy of any type.

Incidence of cardiac toxicity and AML/MDS is listed in Table 4. Cardiac toxicity was rare in all treatment arms, though more frequent among the patients treated with six cycles of AC. Six patients were diagnosed with AML/MDS between 11 and 28 months after initiation of treatment; five in the AC × 6 arm and one in the AC × 4 arm. Patients were 44, 44, 45, 47, 60, and 62 years old at the time of study enrollment. No cases of AML/MDS occurred in patients treated with T.

Causes of death are listed in Table 5. Of 1,578 patients randomly assigned to six cycles of therapy 100 died; 60 as a result of breast cancer–related causes. Of 1,593 patients randomly assigned to the four-cycle arms 91 died; 55 as a result of breast cancer–related causes. There were seven treatment-related deaths, all in the AC study arms; five as a result of AML/MDS and two as a result of cardiac causes.

DISCUSSION

This study examined a head-to-head comparison of four cycles versus six cycles of adjuvant chemotherapy for women with early-stage breast

Table 3. Percentage of Patients With Grade 3 or 4 Adverse Events Observed During Protocol Therapy by Treatment Arm

Adverse Event	Treatment Arm (%)							
	AC × 4 (n = 762)		AC × 6 (n = 751)		T × 4 (n = 769)		T × 6 (n = 759)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hemoglobin	2	0	6	< 1	< 1	0	1	< 1
Neutropenia	9	17	11	23	2	1	2	1
Neutropenia and fever	5	1	6	< 1	< 1	0	0	0
Platelets	1	1	3	1	< 1	0	0	0
Neuropathy								
Sensory	0	0	< 1	0	4	0	10	0
Motor	< 1	0	< 1	0	2	< 1	3	< 1

Abbreviations: AC, doxorubicin and cyclophosphamide; T, paclitaxel.

Table 4. No. of Patients With Grade 3 or Higher Cardiotoxicity or AML/Myelodysplasia Observed After Completing Protocol Therapy by Treatment Arm

	Treatment Arm (No. of patients)											
	AC × 4 (n = 795)			AC × 6 (n = 789)			T × 4 (n = 798)			T × 6 (n = 789)		
Adverse Event	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
LV systolic dysfunction	5	0	0	18	5	1	0	0	0	2	1	0
Restrictive cardiomyopathy	0	0	0	2	1	0	0	0	0	0	0	0
Cardiac, other	0	0	1*	1	0	0	1	0	0	2	0	0
AML/myelodysplasia	0	0	1	0	1	4	0	0	0	0	0	0

Abbreviations: AC, doxorubicin and cyclophosphamide; AML, acute myeloid leukemia; LV, left ventricular; T, paclitaxel.
*Patient died as a result of myocardial infarction.

cancer and zero to three positive axillary nodes. We found that six cycles of a single therapy was not superior to four cycles for either RFS or OS for the overall patient population or in unplanned subset analyses, as defined by ER or HER2 tumor status. In particular, for the 1,126 patients with estrogen-receptor–negative disease, for whom one would expect chemotherapy effect to be most influential on survival, there was no benefit of six cycles of therapy over four cycles.

The study was powered for 567 events but the data were released by the DSMB after 283 events had occurred because a Bayesian methodology indicated that, even if the study continued until all 567 events occurred, the probability of concluding the superiority of six over four cycles was very small ($P = .001$).

Many studies addressing adjuvant therapy in this group of women have tested four cycles versus four cycles or six cycles versus six cycles of different regimens. None have tested four cycles versus six cycles of therapy of the same regimen using the identical dose per cycle and schedule of treatment, which allows for an unconfounded result. Although NSABP B-15 tested four cycles of AC versus six cycles of CMF and found them to be equivalent,[1] some have argued that if AC had been given for six cycles it would have been superior to CMF.

The Breast Intergroup study INT-0102 compared CMF × 6 and CAF × 6, and showed no advantage for CAF over CMF. This study indirectly suggests that CAF × 6 may be equivalent to AC × 4,[4] because both CAF × 6 and AC × 4 are equivalent to CMF (administered with 14 days of oral C, and MF given intravenously on days 1 and 8 of a 28-day cycle). In contrast, the National Cancer Institute of Canada MA.5 trial found cyclophosphamide, epirubicin, and fluorouracil (CEF) × 6 to be superior to CMF × 6, but this study included a different patient mix of only premenopausal women. Further, in the MA.5 study, women with ER-positive tumors did not receive adjuvant hormone therapy.[14] In a subsequent analysis of the data from the MA.5 study, CEF seemed superior only in women with HER2-positive disease who did not receive trastuzumab at the time this trial was conducted.[15]

Table 5. Causes of Death

Treatment Arm	Four Cycles (n = 1,593)	Six Cycles (n = 1,578)	Total (N = 3,171)
Vital status			
Alive	1,502	1,478	2,980
Dead	91	100	191
Cause of death			
Treatment related*	2	5	7
AML	1	4	5
CHF	0	1	1
MI	1	0	1
Breast cancer related	55	60	115
Other†	20	19	39
Unknown‡	14	16	30

NOTE. Table entries are numbers of patients.
Abbreviations: AC, doxorubicin and cyclophosphamide; AML, acute myeloid leukemia; CHF, congestive heart failure; MI, myocardial infarction.
*All treatment-related deaths occurred on the AC study arms.
†Other signifies patients' deaths were related to neither treatment nor disease.
‡Unknown is in addition to Other.

NSABP B-30 compared sequential AC-T (four plus four cycles) versus doxorubicin-docetaxel (four cycles) versus concurrent doxorubicin plus cyclophosphamide plus paclitaxel (four cycles) for women with primary, node-positive breast cancer and found that the sequential AC-T arm yielded better DFS and OS compared with the 4-cycle arms.[16] NSABP B-30 was not a pure comparison of treatment duration because of the differences in the three chemotherapy regimens, including different agents, schedules, and doses. Notably, the longer duration arm in NSABP B-30 was composed of two sequential regimens. The induction of menopause is another possible confounder. NSABP B-30 demonstrated that premenopausal patients with ER-positive tumors who developed amenorrhea had better survival rates than those who continued to menstruate, regardless of which regimen they received. Forty-four percent of the patients on our study were premenopausal at study entry and the data for induction of amenorrhea in these patients remains incomplete. However, one might expect longer duration therapy to induce amenorrhea more frequently than shorter therapy and, therefore, induction of amenorrhea is unlikely to have influenced the results of our study because longer therapy was not associated with better survival.

Therasse et al[17] compared six cycles of CEF administered every 28 days over 6 months versus six cycles of dose-dense epirubicin/cyclophosphamide given every two weeks over 3 months as neoadjuvant therapy in women with locally advanced breast cancer. Outcomes were similar for the two treatment arms that contained different drugs and were given on different schedules, thus not representing a pure duration question.

As one might expect, toxicity was more severe in the six-cycle arms, with a greater incidence of hematologic toxicity in the AC × 6 study arms than in the AC × 4 arms and more neurotoxicity in the T × 6 arms than in the T × 4 arms. Similarly, the occurrence of cardiac toxicity was greater in the AC × 6 study arm when compared with the AC × 4 arm. Although the numbers are small, five of six patients

developed AML/MDS in the AC × 6 arm, but only one patient did so in the AC × 4 arm. The development of AML/MDS is thought to be dependent on dose, and this finding is consistent with that hypothesis.

Our study demonstrates, in a head-to-head comparison, that for women with relatively low-risk primary breast cancer, there is no evidence that extending chemotherapy of AC or single-agent paclitaxel regimens from four to six cycles improves clinical outcome. It should be noted that the 2 × 2 factorial design of this study combines the AC and T groups in the four versus six analysis and, though there was no interaction with type of therapy, single agent T should not be considered a standard regimen for these patients, pending the results of the AC versus T comparison, the results of which are not yet available. It should also be noted that more than 90% of these patients had node-negative disease and 77% had HER2-negative disease. Taking these issues in context, patients can be spared longer and more toxic treatment with these regimens without fear of compromising breast cancer outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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